```
=> b hcaplus
FILE 'HCAPLUS' ENTERED AT 14:24:01 ON 21 MAY 2003
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FILE COVERS 1907 - 21 May 2003  VOL 138 ISS 21
FILE LAST UPDATED: 20 May 2003  (20030520/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d que l23
L13          893 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ANTIVIRAL AGENTS (L)
                 RESISTANCE TO"/CT
L14         1070 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "DRUG RESISTANCE (L) ANTIVIRAL
                 "/CT
L15        14584 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTIVIRAL AGENTS/CT
L16        20690 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DRUG RESISTANCE/CT
L17         1495 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 OR L14 OR (L15 AND L16)
L18          208 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "INFECTION (L) VECTOR"/CT
L19        12094 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PLASMID VECTORS/CT
L20       412389 SEA FILE=HCAPLUS ABB=ON  PLU=ON  GENE/CT
L21         6690 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HEPATITIS C VIRUS+OLD/CT
L22           64 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 AND L21
L23           14 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 AND (L18 OR L19 OR L20)


=> b medline
FILE 'MEDLINE' ENTERED AT 14:24:08 ON 21 MAY 2003

 FILE LAST UPDATED: 20 MAY 2003 (20030520/UP).  FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l40
L28         22575 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANTIVIRAL AGENTS/CT
L29        113043 SEA FILE=MEDLINE ABB=ON  PLU=ON  DRUG RESISTANCE+NT/CT
L31          9146 SEA FILE=MEDLINE ABB=ON  PLU=ON  HEPACIVIRUS/CT
```

```
L32          49 SEA FILE=MEDLINE ABB=ON  PLU=ON  L28 AND L29 AND L31
L40           1 SEA FILE=MEDLINE ABB=ON  PLU=ON  L32 AND VECTOR?


=> d que 142
L28       22575 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANTIVIRAL AGENTS/CT
L29      113043 SEA FILE=MEDLINE ABB=ON  PLU=ON  DRUG RESISTANCE+NT/CT
L31        9146 SEA FILE=MEDLINE ABB=ON  PLU=ON  HEPACIVIRUS/CT
L41          89 SEA FILE=MEDLINE ABB=ON  PLU=ON  L28 AND L29 AND (L31 OR HPC
                  OR HEPATITIS C)
L42           2 SEA FILE=MEDLINE ABB=ON  PLU=ON  L41 AND INDICATOR


=> d que 145
L28       22575 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANTIVIRAL AGENTS/CT
L31        9146 SEA FILE=MEDLINE ABB=ON  PLU=ON  HEPACIVIRUS/CT
L43       13987 SEA FILE=MEDLINE ABB=ON  PLU=ON  DISEASE SUSCEPTIBILITY/CT
L45           0 SEA FILE=MEDLINE ABB=ON  PLU=ON  L28 AND L43 AND (L31 OR HPC
                  OR HEPATITIS C)


=> d que 147
L28       22575 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANTIVIRAL AGENTS/CT
L29      113043 SEA FILE=MEDLINE ABB=ON  PLU=ON  DRUG RESISTANCE+NT/CT
L31        9146 SEA FILE=MEDLINE ABB=ON  PLU=ON  HEPACIVIRUS/CT
L32          49 SEA FILE=MEDLINE ABB=ON  PLU=ON  L28 AND L29 AND L31
L47           8 SEA FILE=MEDLINE ABB=ON  PLU=ON  L32 AND GENE


=> s l40 or l42 or l47
L75          10 L40 OR L42 OR L47

=> b embase
FILE 'EMBASE' ENTERED AT 14:24:37 ON 21 MAY 2003
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 FILE COVERS 1974 TO 19 May 2003 (20030519/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que 159
L48       11166 SEA FILE=EMBASE ABB=ON  PLU=ON  HEPATITIS C VIRUS/CT
L49       16790 SEA FILE=EMBASE ABB=ON  PLU=ON  ANTIVIRUS AGENT/CT
L50       55301 SEA FILE=EMBASE ABB=ON  PLU=ON  DRUG RESISTANCE/CT
L51       31691 SEA FILE=EMBASE ABB=ON  PLU=ON  ANTIBIOTIC RESISTANCE/CT
L56         790 SEA FILE=EMBASE ABB=ON  PLU=ON  DNA VECTOR/CT
L57         830 SEA FILE=EMBASE ABB=ON  PLU=ON  PLASMID VECTOR/CT
L59           0 SEA FILE=EMBASE ABB=ON  PLU=ON  L49 AND (L50 OR L51) AND L48
                  AND (L56 OR L57)


=> d que 169
L48       11166 SEA FILE=EMBASE ABB=ON  PLU=ON  HEPATITIS C VIRUS/CT
L49       16790 SEA FILE=EMBASE ABB=ON  PLU=ON  ANTIVIRUS AGENT/CT
L68        7866 SEA FILE=EMBASE ABB=ON  PLU=ON  VIRUS VECTOR/CT
```

```
L69           2 SEA FILE=EMBASE ABB=ON  PLU=ON  L49 AND L48 AND L68


=> b wpix drugu
FILE 'WPIX' ENTERED AT 14:24:55 ON 21 MAY 2003
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FILE 'DRUGU' ENTERED AT 14:24:55 ON 21 MAY 2003
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=> d que l74
L71       22366 SEA ANTIVIR? OR ANTI VIR?
L72        4934 SEA HEPATITIS C OR HCV OR HEPACVIR?
L73          11 SEA L71 AND L72 AND RESIST?(5A)(VECTOR OR DRUG OR TEST)
L74           7 SEA L73 AND GENE?


=> dup rem l75 l23 l69 l74
FILE 'MEDLINE' ENTERED AT 14:25:14 ON 21 MAY 2003

FILE 'HCAPLUS' ENTERED AT 14:25:14 ON 21 MAY 2003
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FILE 'WPIX' ENTERED AT 14:25:14 ON 21 MAY 2003
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FILE 'DRUGU' ENTERED AT 14:25:14 ON 21 MAY 2003
COPYRIGHT (C) 2003 THOMSON DERWENT
PROCESSING COMPLETED FOR L75
PROCESSING COMPLETED FOR L23
PROCESSING COMPLETED FOR L69
PROCESSING COMPLETED FOR L74
L76           30 DUP REM L75 L23 L69 L74 (3 DUPLICATES REMOVED)

=> d ibib ab hitind l76 1-30

L76  ANSWER 1 OF 30  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2003:334929  HCAPLUS
TITLE:                    A method for identification and development of
                          therapeutic agents
INVENTOR(S):              Mallal, Simon
PATENT ASSIGNEE(S):       Epipop Pty. Ltd., Australia
SOURCE:                   PCT Int. Appl., 157 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
     WO 2003035097      A1   20030501       WO 2002-AU1450    20021023
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: AU 2001-8425 A 20011023

AB The author discloses method(s) for detg. the influence of variation in host genes on selection of microorganisms expressing protein variants for the purpose of therapeutic drug or vaccine design or individualization of such treatment. In one instance, the method comprises identification of HLA allele-specific human immunodeficiency virus sequence polymorphisms that result from HLA restriction of antigen-specific cellular immune responses. It also provides diagnostic and therapeutic methodologies that may be used to measure or treat infection by a microorganism or to prevent infection by the microorganism.

IC ICM A61K038-16
ICS A61K038-17; A61K039-21; A61K039-12; A61P031-18; C07K014-16; C07K014-155

CC 15-1 (Immunochemistry)
Section cross-reference(s): 1

IT INDEXING IN PROGRESS

IT **Gene, animal**
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(HLA-A*2402; of host in relation to immune response-driven antigenic variation in microorganisms)

IT **Gene, animal**
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(HLA-B*0702; of host in relation to immune response-driven antigenic variation in microorganisms)

IT **Gene, animal**
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(HLA-B*1801; of host in relation to immune response-driven antigenic variation in microorganisms)

IT **Gene, animal**
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(HLA-B*4402; of host in relation to immune response-driven antigenic variation in microorganisms)

IT **Gene, animal**
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(HLA-C*0501; of host in relation to immune response-driven antigenic variation in microorganisms)

IT **Gene, animal**
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(HLA-C*0701; of host in relation to immune response-driven antigenic variation in microorganisms)

IT **Gene, animal**
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical

study); BIOL (Biological study)
(HLA-DRB1*0701; of host in relation to immune response-driven antigenic variation in microorganisms)

IT **Gene, animal**
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(HLA-DRB1*1302; of host in relation to immune response-driven antigenic variation in microorganisms)

IT AIDS (disease)
Hepatitis C virus
Human herpesvirus
(detn. of host immune response-driven antigenic variation in microorganisms in relation to)

IT Anti-AIDS agents
Antiviral agents
Drug resistance
Vaccines
(detn. of host immune response-driven antigenic variation in microorganisms in relation to sensitivity to)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(env; detn. of host immune response-driven antigenic variation in microorganisms for therapeutic application)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gag; detn. of host immune response-driven antigenic variation in microorganisms for therapeutic application)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nef; detn. of host immune response-driven antigenic variation in microorganisms for therapeutic application)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pol; detn. of host immune response-driven antigenic variation in microorganisms for therapeutic application)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rev; detn. of host immune response-driven antigenic variation in microorganisms for therapeutic application)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tat; detn. of host immune response-driven antigenic variation in microorganisms for therapeutic application)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vif; detn. of host immune response-driven antigenic variation in microorganisms for therapeutic application)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vpr; detn. of host immune response-driven antigenic variation in

microorganisms for therapeutic application)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vpu; detn. of host immune response-driven antigenic variation in microorganisms for therapeutic application)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L76 ANSWER 2 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:241996 HCAPLUS
DOCUMENT NUMBER: 138:248486
TITLE: Cellular proteins as targets for the treatment of pathogens resistant to drugs that target pathogen-encoded proteins, and use of cdk inhibitors
INVENTOR(S): Schaffer, Priscilla A.; Schang, Luis M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 75 pp., Cont.-in-part of U.S. Ser. No. 951,058.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003060457	A1	20030327	US 2000-905695	20001206
WO 2000006170	A1	20000210	WO 1999-US16252	19990716

W: AU, CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.:

US 1998-94805P	P	19980731
US 1999-131264P	P	19990427
US 1999-140926P	P	19990624
WO 1999-US16252	A1	19990716
US 2000-656592	A2	20000907
US 2000-951058	A2	20000912

AB The invention relates to the identification of cdk inhibitors as inhibitors of gene expression, replication and reactivation in pathogenic agents. Compns. and assays for the identification and use of such inhibitors are provided, as are methods of use of the inhibitors.

IC ICM A61K031-553
ICS A61K031-52; A61K031-4745; A61K031-365; A61K031-404; A61K031-255

NCL 514211080; 514263400; 514456000; 514473000; 514414000; 514285000; 514518000

CC 1-5 (Pharmacology)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICP0; cellular proteins as targets for treatment of pathogens resistant to drugs targeting pathogen-encoded proteins, and use of cdk inhibitors)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICP4; cellular proteins as targets for treatment of pathogens resistant to drugs targeting pathogen-encoded proteins, and use of cdk inhibitors)

IT **Gene, microbial**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICP8; cellular proteins as targets for treatment of pathogens resistant to drugs targeting pathogen-encoded proteins, and use of cdk inhibitors)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TK (thymidine kinase); cellular proteins as targets for treatment of pathogens resistant to drugs targeting pathogen-encoded proteins, and use of cdk inhibitors)

IT **Drug resistance**
(**antiviral**; cellular proteins as targets for treatment of pathogens resistant to drugs targeting pathogen-encoded proteins, and use of cdk inhibitors)

IT AIDS (disease)
Anti-AIDS agents
Antibacterial agents
Antiviral agents
Bactericide resistance
Bovine herpesvirus 1
Cell cycle
Cytomegalovirus
Drug resistance
Drug targets
Equid herpesvirus 1
Fungicide resistance
Fungicides
Hepatitis B virus
Hepatitis C virus
Human
Human T-lymphotropic virus
Human herpesvirus
Human herpesvirus 2
Human herpesvirus 3
Human herpesvirus 4
Human herpesvirus 6
Human herpesvirus 7
Human herpesvirus 8
Human immunodeficiency virus
Human papillomavirus
Parasiticides
Pathogen
Pseudorabies virus
(cellular proteins as targets for treatment of pathogens resistant to drugs targeting pathogen-encoded proteins, and use of cdk inhibitors)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(early; cellular proteins as targets for treatment of pathogens resistant to drugs targeting pathogen-encoded proteins, and use of cdk inhibitors)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gC; cellular proteins as targets for treatment of pathogens resistant to drugs targeting pathogen-encoded proteins, and use of cdk inhibitors)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(immediate early; cellular proteins as targets for treatment of pathogens resistant to drugs targeting pathogen-encoded proteins, and

use of cdk inhibitors)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(late; cellular proteins as targets for treatment of pathogens resistant to drugs targeting pathogen-encoded proteins, and use of cdk inhibitors)

IT **Antiviral agents**
(**resistance to**; cellular proteins as targets for treatment of pathogens resistant to drugs targeting pathogen-encoded proteins, and use of cdk inhibitors)

L76 ANSWER 3 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:98035 HCAPLUS
DOCUMENT NUMBER: 138:131080
TITLE: Compositions and methods for determining susceptibility of hepatitis C virus to antiviral drugs
INVENTOR(S): Parkin, Neil T.; Gamarnik, Andrea
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 43 pp., Cont.-in-part of U.S. Ser. No. 126,559.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003028011	A1	20030206	US 2002-139069	20020503
US 2002034732	A1	20020321	US 1998-126559	19980730
PRIORITY APPLN. INFO.:			US 1997-54257P P	19970730
			US 1998-126559 A2	19980730

AB The invention provides methods for detg. the susceptibility of a pathogenic flavivirus to antiviral compds. This invention also provides methods for detg. antiviral drug susceptibility in a patient infected with a flavivirus. This invention also provides a method for evaluating the biol. effectiveness of a candidate antiviral drug compd. The methods are useful for identifying effective drug regimens for the treatment of flaviviral infections, and identifying and assessing the biol. effectiveness of potential therapeutic compds. Compns. including resistance test vectors and host cells transformed with the resistance test vectors are provided.

IC ICM C12Q001-70
ICS C12Q001-68; C07H021-04; C12N015-00; C12N015-09; C12N015-63; C12N015-70; C12N015-74

NCL 536023720; 435005000; 435006000; 435320100

CC 1-5 (Pharmacology)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(C; compns. and methods for detg. susceptibility of hepatitis C virus to antiviral drugs)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E1; compns. and methods for detg. susceptibility of hepatitis C virus to antiviral drugs)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E2; compns. and methods for detg. susceptibility of hepatitis C virus

to antiviral drugs)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NS2; compns. and methods for detg. susceptibility of hepatitis C virus to antiviral drugs)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NS3; compns. and methods for detg. susceptibility of hepatitis C virus to antiviral drugs)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NS4A; compns. and methods for detg. susceptibility of hepatitis C virus to antiviral drugs)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NS4B; compns. and methods for detg. susceptibility of hepatitis C virus to antiviral drugs)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NS5A; compns. and methods for detg. susceptibility of hepatitis C virus to antiviral drugs)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NS5B; compns. and methods for detg. susceptibility of hepatitis C virus to antiviral drugs)

IT **Antiviral agents**
Hepatitis C virus
Human
Replicon
Viral vectors
(compns. and methods for detg. susceptibility of hepatitis C virus to antiviral drugs)

IT **Drug resistance**
(neomycin resistance-conferring gene; compns. and methods for detg. susceptibility of hepatitis C virus to **antiviral** drugs)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(neomycin resistance-conferring gene; compns. and methods for detg. susceptibility of hepatitis C virus to antiviral drugs)

L76 ANSWER 4 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003159016 EMBASE
TITLE: Inhibition of HCV NS3 protease by RNA aptamers in cells.
AUTHOR: Nishikawa F.; Kakiuchi N.; Funaji K.; Fukuda K.; Sekiya S.; Nishikawa S.
CORPORATE SOURCE: S. Nishikawa, Inst. for Biol. Resources/Functions, National Institute of (AIST), 1-1-1 Higashi, Tsukuba, Ibaraki 305-8566, Japan. satoshi-nishikawa@aist.go.jp
SOURCE: Nucleic Acids Research, (1 Apr 2003) 31/7 (1935-1943).
Refs: 27
ISSN: 0305-1048 CODEN: NARHAD
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
039 Pharmacy

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Non-structural protein 3 (NS3) of hepatitis C virus (HCV) has two distinct activities, protease and helicase, which are essential for HCV proliferation. In previous work, we obtained RNA aptamers (G9-I, II and III) which specifically bound the NS3 protease domain (.DELTA.NS3), efficiently inhibiting protease activity in vitro. To utilize these aptamers in vivo, we constructed a G9 aptamer expression system in cultured cells, using the cytomegarovirus enhancer + chicken .beta.-actin globin (CAG) promoter. By conjugating the cis-acting genomic human hepatitis delta virus (HDV) ribozyme and G9-II aptamer, a chimeric HDV ribozyme-G9-II aptamer (HA) was constructed, which was used to produce stable RNA in vivo and to create tandem repeats of the functional unit. To target the transcribed RNA aptamers to the cytoplasm, the minimal mutant of constitutive transport element (CTE), derived from type D retroviruses, was conjugated at the 3' end of HA (HAC). Transcript RNAs from (HA)(n) and (HAC)(n) were processed into the G9-II aptamer unit by the cis-acting HDV ribozyme, both in vitro and in vivo. Efficient protease inhibition activity of HDV ribozyme-G9-II aptamer expression plasmid was demonstrated in HeLa cells. Protease inhibition activity level of tandem chimeric aptamers, (HA)(n) and (HAC)(n), rose with the increase of n from 1 to 4.

CT Medical Descriptors:
Hepatitis C virus
enzyme inhibition
enzyme activity
in vivo study
gene construct
gene expression
cell culture
Cytomegalovirus
enhancer region
promoter region
human genome
Hepatitis delta virus
RNA stability
tandem repeat
gene function
gene targeting
RNA transcription
mutant
Retrovirus
in vitro study
plasmid
virus vector
viral gene delivery system
antiviral activity
human
nonhuman
controlled study
human cell
review
priority journal
Drug Descriptors:
*protein NS3: EC, endogenous compound
*virus protein: EC, endogenous compound
*virus RNA: EC, endogenous compound
*aptamer: PR, pharmaceutics
*aptamer: PD, pharmacology

proteinase: EC, endogenous compound
helicase: EC, endogenous compound
beta actin: EC, endogenous compound
globin: EC, endogenous compound
ribozyme: EC, endogenous compound
chimeric protein: EC, endogenous compound
cis acting element: EC, endogenous compound
proteinase inhibitor: PR, pharmaceutics
proteinase inhibitor: PD, pharmacology
antivirus agent: PR, pharmaceutics
antivirus agent: PD, pharmacology
unclassified drug
RN (proteinase) 9001-92-7; (helicase) 42613-29-6; (proteinase inhibitor) 37205-61-1

L76 ANSWER 5 OF 30 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:221147 HCAPLUS
DOCUMENT NUMBER: 136:241622
TITLE: Compositions and methods for determining anti-viral drug susceptibility and resistance and anti-viral drug screening
INVENTOR(S): Capon, Daniel J.; Whitcomb, Jeannette M.; Parkin, Neil T.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 48 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002034732	A1	20020321	US 1998-126559	19980730
US 2003028011	A1	20030206	US 2002-139069	20020503

PRIORITY APPLN. INFO.: US 1997-54257P P 19970730
US 1998-126559 A2 19980730

AB This invention provides a method for detg. susceptibility for an hepatitis C virus (HCV) or human cytomegalovirus (HCMV) anti-viral drug comprising: (a) introducing a resistance test vector comprising a patient-derived segment and an indicator gene into a host cell; (b) culturing the host cell from (a); (c) measuring expression of the indicator gene in a target host cell; and (d) comparing the expression of the indicator gene from (c) with the expression of the indicator gene measured when steps (a)-(c) are carried out in the absence of the anti-viral drug, wherein a test concn. of the anti-viral drug is present at steps (a)-(c); at steps (b)-(c); or at step (c). This invention also provides a method for detg. HCV or HCMV anti-viral drug resistance in a patient comprising: (a) detg. anti-viral drug susceptibility in the patient at a first time using the susceptibility test described above, wherein the patient-derived segment is obtained from the patient at about said time;(b) detg. anti-viral drug susceptibility of the same patient at a later time; and (c) comparing the anti-viral drug susceptibilities detd. in step (a) and (b) wherein a decrease in anti-viral drug susceptibility at the later time compared to the first time indicates development or progression of anti-viral drug resistance in the patient. This invention also provides a method for evaluating the biol. effectiveness of a candidate HCV or HCMV anti-viral drug compd. Compns. including resistance test vectors comprising a

patient-derived segment comprising a HCV or HCMV gene and an indicator gene and host cells transformed with the resistance test vectors are provided.

IC ICM C12Q001-70
ICS C12Q001-68; C12Q001-18; C12P013-14; C12N001-20; C12N015-00; C12N015-09; C12N015-63; C12N015-70; C12N015-74

NCL 435005000

CC 1-1 (Pharmacology)
Section cross-reference(s): 3

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(UL, resistance test vector comprising; compns. and methods for detg. anti-viral drug susceptibility and resistance and anti-viral drug screening)

IT Antiviral agents
Fibroblast
Genetic vectors
Hepatitis C virus
Human
Human herpesvirus 5
Transformation, genetic
(compns. and methods for detg. anti-viral drug susceptibility and resistance and anti-viral drug screening)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(compns. and methods for detg. anti-viral drug susceptibility and resistance and anti-viral drug screening)

IT **Gene**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(indicator; compns. and methods for detg. anti-viral drug susceptibility and resistance and anti-viral drug screening)

IT **Antiviral agents**
(**resistance to**; compns. and methods for detg. anti-viral drug susceptibility and resistance and anti-viral drug screening)

L76 ANSWER 6 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:869219 HCAPLUS
DOCUMENT NUMBER: 137:363028
TITLE: Drug screening assays and kits for discovery of anti-microbial and chemotherapeutics agents
INVENTOR(S): McCarthy, Lawrence; Kong, Lilly; Shao, Tang; Su, Xin
PATENT ASSIGNEE(S): Focus Technologies, Inc., USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002090993	A2	20021114	WO 2001-US44783	20011127

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,

UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003039957 A1 20030227 US 2001-996187 20011127

PRIORITY APPLN. INFO.: US 2000-253150P P 20001127
US 2001-304533P P 20010709
US 2001-297686P P 20010712
US 2001-996187 A2 20011127

AB Methods and compns. for detecting the phenotype of a bioactive mol. assays. More specifically, are provided methods and compns. are provided for detg. the suitability of one ore more candidate compds. prior to or during the course of chemotherapy or anti-infective therapy, for their capacity to inhibit the bioactive mols. of micro-organisms, cancers and as an assay for expression in transgene therapy. Also provided are phenotypic assays for drug discovery. Claimed sequences were not present at the time of publication.

IC ICM G01N033-68
ICS G01N033-569; C12Q001-68

CC 1-1 (Pharmacology)
Section cross-reference(s): 3, 9

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NS5b, of HCV, screening for; drug screening assays for discovery of anti-microbial and chemotherapeutics agents)

IT **Gene, animal**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VLA-4, screening for effectors of; drug screening assays for discovery of anti-microbial and chemotherapeutics agents)

IT Carbohydrates, biological studies
Chemokines
Cytokines
Enzymes, biological studies
Gene
Glycoproteins
Hormones, animal, biological studies
Lipopolysaccharides
Lipoproteins
Lymphokines
Mucopolysaccharides, biological studies
Nucleoside analogs
Peptides, biological studies
Polysaccharides, biological studies
Proteins
rRNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(as bioactive mol., screening for; drug screening assays for discovery of anti-microbial and chemotherapeutics agents)

IT Adenoviridae
Animal
Antibacterial agents
Antitumor agents
Antiviral agents
Aspergillus
Bacillus (bacterium genus)
Bacteria (Eubacteria)
Basidiobolus
Blastomyces

Brucella
Candida
Chlamydia
Clostridium
Coccidioides
Conidiobolus
Coronavirus
Cryptococcus (fungus)
Cryptosporidium
Cunninghamella
Drug screening
Enterobacteriaceae
Enterococcus
Epidermophyton
Flavivirus
Francisella
Fungi
Fungicides
Fusarium
Hantavirus
Hepatitis B virus
Hepatitis C virus
Hepatitis virus
Herpesviridae
Histoplasma
Human
Human herpesvirus 5
Human immunodeficiency virus 1
Human immunodeficiency virus 2
Influenza virus
Listeria
Malassezia
Microsporum
Mucor
Mycobacterium
Mycoplasma
Neisseria
Orthomyxovirus
Paecilomyces
Paracoccidioides
Paramyxovirus
Pasteurella
Penicillium
Picornaviridae
Plasmodium (malarial genus)
Pneumocystis
Poxviridae
Protozoa
Protozoacides
Pseudallescheria
Pseudomonas
Retroviridae
Rhinosporidium
Rhizopus
Salmonella
Shigella
Sporothrix
Staphylococcus

Streptococcus
Test kits
Trichophyton
Trypanosoma
Vibrio
Virus
Yersinia
(drug screening assays for discovery of anti-microbial and chemotherapeutics agents)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gyrA, screening for effectors of; drug screening assays for discovery of anti-microbial and chemotherapeutics agents)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gyrB, screening for effectors of; drug screening assays for discovery of anti-microbial and chemotherapeutics agents)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(parC, screening for effectors of; drug screening assays for discovery of anti-microbial and chemotherapeutics agents)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(parE, screening for effectors of; drug screening assays for discovery of anti-microbial and chemotherapeutics agents)

IT **Drug resistance**
(screening; drug screening assays for discovery of anti-microbial and chemotherapeutics agents)

L76 ANSWER 7 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:521407 HCAPLUS
DOCUMENT NUMBER: 137:73237
TITLE: Single and combination therapy using drugs with target cellular proteins and drugs which target pathogen-encoded proteins
INVENTOR(S): Schaffer, Priscilla A.; Schang, Luis M.
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 153 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053096	A2	20020711	WO 2001-US47257	20011206
WO 2002053096	A3	20030130		

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: US 2000-251623P P 20001206
US 2000-251653P P 20001206

AB The invention relates to the identification of cdk inhibitors as inhibitors of pathogen gene expression, replication and reactivation. The invention also relates to the identification of a combination therapy to inhibit pathogen replication in which a drug that inhibits pathogen replication by targeting a specific pathogen-encoded protein is

administered in combination with a drug that inhibits pathogen replication by targeting host-encoded cdk proteins. Compns. and assays for the identification and use of such inhibitors are provided as are methods of use of the inhibitors.

IC ICM A61K

CC 1-5 (Pharmacology)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GAPDH; drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICP0; drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICP22; drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICP27; drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICP4; drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICP8; drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

IT Anti-AIDS agents
Anti-infective agents
Antibacterial agents
Antiviral agents
Bacteria (Eubacteria)
Bovine herpesvirus 1
Cell cycle
Cytomegalovirus
Drug interactions
Drug resistance
Equid herpesvirus 1
Fungi
Fungicides
Hepatitis B virus
Hepatitis C virus
Herpesviridae
Human
Human T-lymphotropic virus
Human herpesvirus
Human herpesvirus 1
Human herpesvirus 2
Human herpesvirus 3
Human herpesvirus 4
Human herpesvirus 6
Human herpesvirus 7
Human herpesvirus 8
Human immunodeficiency virus
Human papillomavirus

Infection
Parasite
Parasiticides
Pseudorabies virus
Transcription, genetic
Virus
Yeast
(drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(early; drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gC; drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(immediate early; drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(late; drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tk; drugs with target cellular proteins and drugs which target pathogen-encoded proteins for single and combination therapy)

L76 ANSWER 8 OF 30 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-292269 [33] WPIX
DOC. NO. CPI: C2002-085924
TITLE: New polynucleotides, useful to detect extrachromosomal molecules and screening for modulating agents e.g. anticancer agents, comprises extrachromosomal molecule operably linked to tag.
DERWENT CLASS: B04 D16
INVENTOR(S): FASEL-OTTER, M; KANDA, T; WAHL, G M
PATENT ASSIGNEE(S): (SALK) SALK INST BIOLOGICAL STUDIES
COUNTRY COUNT: 97
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002020823	A2	20020314	(200233)*	EN	55

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001088918 A 20020322 (200251)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 2002020823 A2 WO 2001-US28130 20010907
AU 2001088918 A AU 2001-88918 20010907

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001088918 A	Based on	WO 200220823

PRIORITY APPLN. INFO: US 2000-230730P 20000907

AB WO 200220823 A UPAB: 20020524

NOVELTY - A preselected nucleic acid molecule (I) comprising an extrachromosomal molecule (i.e. a molecule that segregates with cellular chromosomes and is tethered to a cellular chromatid during cell division) operably linked to a tag enabling detection of the extrachromosomal molecule, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a preselected molecule (II) comprising a reporter **gene** fused to a lac repressor-nuclear localization signal;

(2) a vector (III) comprising a histone H2B **gene** fused to a reporter **gene**;

(3) a recombinant tethering polypeptide (IV);

(4) a cell (V) comprising the nucleic acid molecule, vector or polypeptide;

(5) interfering with chromosomal tethering of extrachromosomal molecule by contacting (III) with a cell suspected of containing an extrachromosomal molecule;

(6) identifying at least one agent that modulates chromosomal tethering of an extrachromosomal molecule;

(7) treating cancer comprising administering a pharmaceutical composition comprising a compound that inhibits tethering of an extrachromosomal molecule to a chromosome;

(8) treating a viral infection comprising administering a pharmaceutical composition comprising a compound that inhibits tethering of an viral extrachromosomal molecule to a chromosome;

(9) identifying an **antiviral**/anticancer agent;

(10) a chromosomally integrating vector that specifically labels double-minute chromosomes (DMs); and

(11) a plasmid vector comprising:

(a) retroviral vector, a **gene** encoding green fluorescent protein (GFP) fused to lac repressor-nuclear localization signal;

(b) retroviral vector, a **gene** encoding yellow fluorescent protein (YFP) fused to lac repressor-nuclear localization signal; or

(c) a histone H2B **gene** and a cyano fluorescent protein.

ACTIVITY - Cytostatic; **Antiviral**.

MECHANISM OF ACTION - Inhibitors of chromosomal tethering of extrachromosomal molecules. No supporting data is given in the source material.

USE - The polynucleotides are useful to visualize chromosomal tethering of extrachromosomal molecules in cells, useful diagnostically since extrachromosomal molecules are known to encode oncogenes and **drug resistance genes** linked to proliferative disorders. They also enable interference with such tethering, useful to treat cancer, viral infections or other conditions involving extrachromosomal molecules. The vectors may similarly be used to visualize and/or interfere with chromosomal tethering of extrachromosomal molecules (especially double minute chromosomes/viruses) in cells. The

polynucleotides, cells, vectors and polypeptides are also useful to identify agents modulating chromosomal tethering of extrachromosomal agents, especially **antiviral** agents or anticancer agents. Compounds inhibiting tethering may then be administered in pharmaceutical compositions to treat cancer or viral infections.
Dwg.0/7

L76 ANSWER 9 OF 30 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-280605 [32] WPIX
DOC. NO. CPI: C2002-082528
TITLE: Novel nucleic acid construct useful for detecting the presence of RNA virus, comprises an expression cassette and a promoter operably linked to expression cassette for minus strand RNA transcription of the cassette.
DERWENT CLASS: B04 D16
INVENTOR(S): HONG, W J; LIM, S G; LIM, S P; TAN, Y H
PATENT ASSIGNEE(S): (EHRL-I) EHRLICH G; (MOLE-N) INST MOLECULAR & CELL BIOLOGY
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002008447	A2	20020131	(200232)*	EN	81
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001082417	A	20020205	(200236)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002008447	A2	WO 2001-IL669	20010720
AU 2001082417	A	AU 2001-82417	20010720

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001082417	A	Based on	WO 200208447

PRIORITY APPLN. INFO: US 2000-220248P 20000724
AB WO 200208447 A UPAB: 20020521
NOVELTY - Nucleic acid construct (I) comprises expression cassette (II) having 3 polynucleotide regions (P1,P2,P3) and promoter operably linked to (II) for minus strand RNA transcription of (II).
DETAILED DESCRIPTION - (I) comprises an expression cassette (II) including a first polynucleotide region (P1) including a 5' non-coding region (NCR) sequence of an RNA virus and at least an N-terminal portion of a coding sequence of RNA virus, a second polynucleotide region (P2) including a 3' untranslated region (UTR) sequence of the RNA virus and at least a C-terminal portion of a coding sequence of the virus, and a third polynucleotide region (P3) encoding a reporter molecule, flanked by P1 and P2, and a promoter sequence being operatively linked to (II) in a manner

so as to enable a transcription of a minus strand RNA molecule from (II).

An INDEPENDENT CLAIM is also included for a **genetically** transformed cell (III) comprising (I).

USE - (I) is useful for detecting the presence of an RNA virus in a cell, by incubating (I) with an extract of the cell under conditions suitable for transcription and translation of (I), or expressing a nucleic acid construct with the cell, quantifying the level of reporter molecule to determine the presence of virus in the cell, and comparing the level of the reporter molecule to that obtained from cells free of virus. (I) is also useful for screening **anti-viral drugs** and determining **drug resistance** of an RNA virus, by co-incubating (I), a polynucleotide encoding at least a polymerase of a RNA virus and a potential **anti-viral** molecule (e.g. nucleoside, nucleotide analog and an immune-modulatory molecule) or drug under conditions suitable for transcription and translation of (I) and a polynucleotide encoding the polymerase, and quantifying the level of reporter molecule (all claimed).

ADVANTAGE - (I) provides an accurate and rapid cell-based assays for detecting **HCV** infections, screening molecules for potential **antiviral** activities and determining **drug resistance** of **HCV** molecules.

DESCRIPTION OF DRAWING(S) - The figure shows the **generation** of chimeric antisense expression constructs pAS9 and pAS11, and their sense-oriented counterparts.

Dwg.1b/3

L76 ANSWER 10 OF 30 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002322107 MEDLINE
DOCUMENT NUMBER: 22059425 PubMed ID: 12064791
TITLE: Analysis of sequence configurations of the ISDR, PKR-binding domain, and V3 region as predictors of response to induction interferon-alpha and ribavirin therapy in chronic hepatitis C infection.
AUTHOR: Murphy Melissa D; Rosen Hugo R; Marousek Gail I; Chou Sunwen
CORPORATE SOURCE: Medical and Research Services, Portland VA Medical Center, Oregon 97201, USA.
SOURCE: DIGESTIVE DISEASES AND SCIENCES, (2002 Jun) 47 (6) 1195-205.
Journal code: 7902782. ISSN: 0163-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020615
Last Updated on STN: 20020626
Entered Medline: 20020625

AB Interferon (IFN) and ribavirin combination therapy for chronic hepatitis C virus (HCV) infection yields a sustained response rate of only approximately 40%. Previous studies have linked IFN responsiveness to viral sequence variation in parts of the E2 and NS5A **genes**, but this remains controversial. We studied pretreatment sera from 28 subjects (23 with HCV genotype 1a) who received high-dose IFN induction followed by IFN-ribavirin combination therapy. Serum HCV sequences were amplified and compared from 14 responders with undetectable HCV RNA 24 weeks after therapy and 11 nonresponders (excluding three who dropped out of the study). Analysis included the E2 PKR eIF-2alpha phosphorylation homology

domain (PePHD, codons 659-670), where the sequence was well conserved, and codons 2001-2420 of NS5A. In NS5A, the proposed PKR binding domain (codons 2209-2274), containing the putative IFN sensitivity determining region (ISDR, codons 2209-2248), showed too little variation among subjects to differentiate responders and nonresponders. NS5A codons 2356-2385 (which includes the V3 region) exhibited more variation. Here, six of 12 genotype 1a responders showed four or more amino acid changes from the prototype HCV-1 sequence, as compared with one of eight nonresponders, but this fell short of statistical significance (P = 0.16). NS5A sequences from posttreatment sera were examined in six nonresponders to look for selection of treatment-resistant viral subpopulations, but no consistent change was detected. In conclusion, our results indicate that the sequences of the ISDR, the PKR-binding domain, and the PePHD are unlikely to have predictive value for IFN treatment success in those infected with HCV genotype 1a. However, the finding of greater variability among treatment responders in the carboxy end of NS5A suggests that the V3 region merits further investigation.

CT Check Tags: Female; Human; Male; Support, U.S. Gov't, Non-P.H.S.
Adult
Amino Acid Sequence: GE, genetics
Antiviral Agents: AD, administration & dosage
***Antiviral Agents: TU, therapeutic use**
Codon
Drug Resistance, Viral
Drug Therapy, Combination
*Eukaryotic Initiation Factor-2: GE, genetics
Genotype
Hepacivirus: DE, drug effects
***Hepacivirus: GE, genetics**
Hepatitis C Antigens: GE, genetics
*Hepatitis C, Chronic: DT, drug therapy
Hepatitis C, Chronic: GE, genetics
*Hepatitis C, Chronic: VI, virology
Interferon-alpha: AD, administration & dosage
*Interferon-alpha: TU, therapeutic use
Middle Age
Phosphorylation
RNA, Viral: AN, analysis
Ribavirin: AD, administration & dosage
*Ribavirin: TU, therapeutic use
Sequence Homology, Amino Acid
Treatment Outcome
*Viral Envelope Proteins: GE, genetics
*eIF-2 Kinase: GE, genetics

RN 36791-04-5 (Ribavirin)

CN 0 (Antiviral Agents); 0 (Codon); 0 (Eukaryotic Initiation Factor-2); 0 (Hepatitis C Antigens); 0 (Interferon-alpha); 0 (RNA, Viral); 0 (Viral Envelope Proteins); EC 2.7.1.37 (eIF-2 Kinase)

L76 ANSWER 11 OF 30 MEDLINE
ACCESSION NUMBER: 2002317052 MEDLINE
DOCUMENT NUMBER: 22055363 PubMed ID: 12060493
TITLE: Induction of IL-1Ra in resistant and responsive **hepatitis C** patients following treatment with IFN-con1.
AUTHOR: Cotler Scott J; Craft Teresa; Ferris Mary; Morrisey Mary; McCone Jonathan; Reddy K Raj; Conrad Andrew; Jensen Donald M; Albrecht Jeff; Taylor Milton W

CORPORATE SOURCE: Section of Hepatology and Department of Preventive Medicine, RUSH-Presybterian-St. Luke's Medical Center, Chicago, IL 60612, USA.
SOURCE: JOURNAL OF INTERFERON AND CYTOKINE RESEARCH, (2002 May) 22 (5) 549-54.
Journal code: 9507088. ISSN: 1079-9907.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20020613
Last Updated on STN: 20021217
Entered Medline: 20021204

AB **Hepatitis C** virus (HCV) infection is resistant to interferon-alpha (IFN-alpha) in some patients. The mechanism of this resistance is unknown. Interleukin-1 receptor antagonist (IL-1Ra) is induced by IFN-alpha and is a good **indicator** of IFN activity. In the current study, we compared IL-1Ra levels in rapid virologic responders and flat responders who showed resistance to IFN. Three groups of patients were examined, including those who received a single dose of consensus IFN (IFN-con1), patients who received daily IFN-con1 for 1 week, and patients who received IFN-con1 daily for 24 weeks. Serum IL-1Ra, IL-6, and HCV RNA were measured serially in all groups. Serum IL-1Ra levels increased rapidly in all patients with **hepatitis C** after IFN-alpha administration, irrespective of their virologic response. IL-1Ra levels remained elevated at 1 week but were similar to baseline by week 2 of treatment in patients receiving continuous therapy. IL-6 levels also increased acutely but rose more slowly than IL-1Ra levels. The increase in IL-1Ra and IL-6 observed in both flat and rapid virologic responders indicates that IFN receptors are functioning in patients with IFN-resistant **hepatitis C** and that the lack of response is related to other virologic or immunologic factors.

CT Check Tags: Human
Adult
Aged
***Antiviral Agents: TU, therapeutic use**
Drug Resistance, Viral
Hepacivirus: DE, drug effects
Hepacivirus: IP, isolation & purification
***Hepatitis C, Chronic: DT, drug therapy**
***Hepatitis C, Chronic: IM, immunology**
Hepatitis C, Chronic: VI, virology
*Interferon Type I, Recombinant: TU, therapeutic use
Middle Age
RNA, Viral: BL, blood
*Sialoglycoproteins: BI, biosynthesis
Sialoglycoproteins: BL, blood
Viremia: DT, drug therapy
Viremia: IM, immunology
Viremia: VI, virology

RN 118390-30-0 (interferon alfacon-1)
CN 0 (Antiviral Agents); 0 (Interferon Type I, Recombinant); 0 (RNA, Viral); 0 (Sialoglycoproteins); 0 (interleukin 1 receptor antagonist protein)

L76 ANSWER 12 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:223116 HCAPLUS
DOCUMENT NUMBER: 137:153164

TITLE: Polymorphisms in the interleukin-10, tumor necrosis factor-.alpha., and transforming growth factor-.beta.1 genes in chronic hepatitis C patients treated with interferon and ribavirin

AUTHOR(S): Vidigal, Pedro G.; Germer, Jeffrey J.; Zein, Nizar N.
CORPORATE SOURCE: Division of Gastroenterology, Hepatology and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, MN, USA

SOURCE: Journal of Hepatology (2002), 36(2), 271-277
CODEN: JOHEEC; ISSN: 0168-8278
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In hepatitis C infection, the prodn. of inappropriate cytokine levels appears to contribute to viral persistence and to affect the response to antiviral therapy. Addnl., polymorphisms in the cytokine genes may affect the prodn. of the cytokines. In this study, we detd. the frequency of the genotypes assocd. with polymorphisms of the interleukin-10 and tumor necrosis factor-.alpha. gene promoters, and transforming growth factor-.beta.1 gene leader sequence, and investigated their assocn. with clin. features and the response to interferon-.alpha. and ribavirin therapy in chronic hepatitis C infection. Genomic DNA from 80 patients and 37 racially matched healthy controls was studied by polymerase chain reaction and direct automated sequencing. The interleukin-10 - 1082 G/G genotype was identified more frequently in patients than in controls (P = 0.048). The transforming-growth factor-.beta.1 +29 (codon 10) C/C genotype was assocd. with resistance to the therapy (P = 0.029). After adjusting for potential confounding variables, patients exhibiting the C/C genotype were less likely to respond to treatment than patients with the T/T or T/C genotypes. These results suggest that inheritance of the interleukin-10 - 1082 G/G and the transforming growth factor-.beta.1 +29 C/C genotypes, which appear to affect the cytokine prodn., may be assocd. with susceptibility to chronic hepatitis C infection and resistance to combined antiviral therapy.

CC 14-3 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 1, 2, 3, 15

IT **Gene, animal**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(IL-10; interleukin-10, TNF-.alpha., and TGF-.beta.1 genes polymorphisms in chronic hepatitis C patients treated with interferon and ribavirin and resistance to therapy)

IT **Gene, animal**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(TGF-.beta.1; interleukin-10, TNF-.alpha., and TGF-.beta.1 genes polymorphisms in chronic hepatitis C patients treated with interferon and ribavirin and resistance to therapy)

IT **Gene, animal**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(TNFA; interleukin-10, TNF-.alpha., and TGF-.beta.1 genes polymorphisms in chronic hepatitis C patients treated with interferon and ribavirin and resistance to therapy)

IT **Drug resistance**
(**antiviral**; interleukin-10, TNF-.alpha., and TGF-.beta.1 genes polymorphisms in chronic hepatitis C patients treated with interferon and ribavirin and resistance to therapy)

IT Genetic polymorphism
Genotypes
Hepatitis C virus
Human
Susceptibility (genetic)
(interleukin-10, TNF-.alpha., and TGF-.beta.1 genes polymorphisms in chronic hepatitis C patients treated with interferon and ribavirin and resistance to therapy)
IT **Antiviral agents**
(**resistance to**; interleukin-10, TNF-.alpha., and TGF-.beta.1 genes polymorphisms in chronic hepatitis C patients treated with interferon and ribavirin and **resistance to** therapy)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L76 ANSWER 13 OF 30 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-147445 [19] WPIX
DOC. NO. CPI: C2002-045622
TITLE: Detecting minority genomes in viral quasi-species, useful for identifying mutants responsible for **drug resistance** and to individualize therapy.
DERWENT CLASS: A96 B04 D16
INVENTOR(S): ARIAS ESTEBAN, A; BARANOWSKI, E; BRIONES LLORENTE, C; DOMINGO SOLANS, E; ESCARMIS HOMS, C; GOMEZ CASTILLA, J; MARTIN RUIZ-JARABO, C; PARRO GARCIA, V
PATENT ASSIGNEE(S): (CNSJ) CONSEJO SUPERIOR INVESTIGACIONES CIENTIF
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001083815	A1	20011108	(200219)*	ES	106
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001056362	A	20011112	(200222)		
EP 1284296	A1	20030219	(200321)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001083815	A1	WO 2001-ES165	20010427
AU 2001056362	A	AU 2001-56362	20010427
EP 1284296	A1	EP 2001-929654	20010427
		WO 2001-ES165	20010427

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001056362	A Based on	WO 200183815

EP 1284296 A1 Based on WO 200183815

PRIORITY APPLN. INFO: ES 2000-1068 20000427

AB WO 200183815 A UPAB: 20020321
NOVELTY - Detecting minority genomes (MG), present at less than 50 %, in a population of nucleic acids (NA) of a viral quasi-species (VQS) and having at least one mutation with respect to the majority genome, is new.
DETAILED DESCRIPTION - Detecting minority genomes (MG), present at less than 50 %, in a population of nucleic acids (NA) of a viral quasi-species (VQS) and having at least one mutation with respect to the majority genome, is new. NA of VQS is extracted from a suspect sample, at least one fragment of it is amplified and MG detected and analyzed using DNA microchip techniques, heteroduplex fingerprinting and molecular cloning.
An INDEPENDENT CLAIM is also included for kits for detecting MG.
USE - For **genetic** diagnosis of viral infections, especially human immune deficiency virus and hepatitis B or C, particularly to detect 'memory' minority genomes that are implicated in failure of **antiviral** therapy, so the method may make possible design of therapies customized for individual patients.
Dwg.0/5

L76 ANSWER 14 OF 30 MEDLINE
ACCESSION NUMBER: 2001667757 MEDLINE
DOCUMENT NUMBER: 21570393 PubMed ID: 11713272
TITLE: Involvement of proteasome alpha-subunit PSMA7 in hepatitis C virus internal ribosome entry site-mediated translation.
AUTHOR: Kruger M; Beger C; Welch P J; Barber J R; Manns M P; Wong-Staal F
CORPORATE SOURCE: Department of Medicine, University of California-San Diego, 9500 Gilman Dr., La Jolla, CA 92093-0665, USA.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2001 Dec) 21 (24) 8357-64. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011120
Last Updated on STN: 20020123
Entered Medline: 20011221

AB Ribozymes are small catalytic RNA molecules that can be engineered to enzymatically cleave RNA transcripts in a sequence-specific fashion and thereby inhibit expression and function of the corresponding **gene** product. With their simple structures and site-specific cleavage activity, they have been exploited as potential therapeutic agents in a variety of human disorders, including hepatitis C virus (HCV) infection. We have designed a hairpin ribozyme (Rz3'X) targeting the HCV minus-strand replication intermediate at position 40 within the 3'X tail. Surprisingly, Rz3'X was found to induce ganciclovir (GCV)-resistant colonies in a bicistronic cellular reporter system with HCV internal ribosome entry site (IRES)-dependent translation of herpes simplex virus thymidine kinase (TK). Rz3'X-transduced GCV-resistant HeLa reporter cells showed substantially reduced IRES-mediated HCV core protein translation compared with control **vector**-transduced cells. Since these reporter systems do not contain the HCV 3'X tail sequences, the results indicate that Rz3'X probably exerted an inhibitory effect on HCV IRES activity fortuitously through another **gene** target. A novel

technique of ribozyme cleavage-based target **gene** identification (cleavage-specific amplification of cDNA ends) (M. Kruger, C. Beger, P. J. Welch, J. R. Barber, and F. Wong-Staal, Nucleic Acids Res. 29:e94, 2001) revealed that human 20S proteasome alpha-subunit PSMA7 mRNA was a target RNA recognized and cleaved by Rz3'X. We then showed that additional ribozymes directed against PSMA7 RNA inhibited HCV IRES activity in two assay systems: GCV resistance in the HeLa IRES TK reporter cell system and a transient transfection assay performed with a bicistronic Renilla-HCV IRES-firefly luciferase reporter in Huh7 cells. In contrast, ribozymes were inactive against IRES of encephalomyocarditis virus and human rhinovirus. Additionally, proteasome inhibitor MG132 exerted a dose-dependent inhibitory effect on HCV IRES-mediated translation but not on cap-dependent translation. These data suggest a principal role for PSMA7 in regulating HCV IRES activity, a function essential for HCV replication.

CT Check Tags: Human; Support, Non-U.S. Gov't
Antiviral Agents: PD, pharmacology
Binding Sites
Blotting, Northern
Blotting, Western
*Cysteine Endopeptidases: CH, chemistry
*Cysteine Endopeptidases: ME, metabolism
Dose-Response Relationship, Drug
Drug Resistance
Ganciclovir: PD, pharmacology
Hela Cells
***Hepacivirus: ME, metabolism**
Luciferase: ME, metabolism
Models, Genetic
*Multienzyme Complexes: CH, chemistry
*Multienzyme Complexes: ME, metabolism
Plasmids: ME, metabolism
Protein Binding
*Protein Subunits
RNA, Catalytic: ME, metabolism
RNA, Messenger: ME, metabolism
Retroviridae: GE, genetics
Thymidine Kinase: ME, metabolism
Transduction, Genetic
Transfection
*Translation, Genetic
Tumor Cells, Cultured

RN 82410-32-0 (Ganciclovir)

CN 0 (Antiviral Agents); 0 (Multienzyme Complexes); 0 (Plasmids); 0 (Protein Subunits); 0 (RNA, Catalytic); 0 (RNA, Messenger); EC 1.13.12.- (Luciferase); EC 2.7.1.21 (Thymidine Kinase); EC 3.4.22 (Cysteine Endopeptidases); EC 3.4.99.46 (multicatalytic endopeptidase complex)

L76 ANSWER 15 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:41205 HCAPLUS
DOCUMENT NUMBER: 135:120985
TITLE: Method to detect substitutions in the interferon-sensitivity-determining region of hepatitis C virus 1b for prediction of response to interferon therapy
AUTHOR(S): Nishiguchi, Shuhei; Ueda, Tadashi; Itoh, Teiji; Enomoto, Masaru; Tanaka, Motoharu; Tatsumi, Nobuyuki; Fukuda, Katsuhiko; Tamori, Akihiro; Habu, Daiki;

Takeda, Tadashi; Otani, Shuzo; Shiomi, Susumu
CORPORATE SOURCE: Third Department of Internal Medicine, Osaka City University Medical School, Osaka, 545-8586, Japan
SOURCE: Hepatology (Philadelphia) (2001), 33(1), 241-247
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Substitutions deduced by direct sequencing in the interferon-sensitivity-detg. region (ISDR) of hepatitis C virus (HCV) are related to patients' responses to interferon (IFN), but sequencing is time consuming and results are only for the dominant virus. We developed a rapid method to detect such changes. With serum from 50 patients with chronic hepatitis C (genotype 1b) given IFN-.alpha., a way to detect changes in ISDR by hybridization with oligonucleotide probes that had a prototype nucleotide sequence of HCV-J was established. Hybridization intensity was expressed as optical d. The method was checked with serum from 100 more patients. In the study of 50 patients, all 21 with the prototype sequences had a high OD. (.gtoreq.0.4), and all 8 patients with a mutant-type sequence had low values (.ltoreq.0.2). Twelve (95% confidence interval, 36-81%) of 20 patients with OD of <0.4 and 2 (1%-22%) of 30 patients with OD .gtoreq.0.4 had complete responses (CR). All nine (66%-100%) patients with OD <0.4 and little HCV RNA (<100 kIU/mL) had CR, but none (0%-14%) of the 24 patients with high values from both predictors had CR. In the study of 100 patients, OD and the HCV RNA level were independent predictors of the effects of IFN. By multivariate anal., the odds ratio for a CR in patients with ODNS5A of .gtoreq.0.4 was 0.015 (0.001-0.190) compared with the other patients (P = .001). In conclusion, our method should be useful in identification of prototype strains, which generally resist IFN therapy.
CC 15-5 (Immunochemistry)
Section cross-reference(s): 1, 3
IT **Drug resistance**
(**antiviral;** method to detect substitutions in interferon-sensitivity-detg. region of hepatitis C virus 1b for prediction of response to interferon therapy in humans)
IT Genotypes
Hepatitis C virus
Mutation
Protein sequences
(method to detect substitutions in interferon-sensitivity-detg. region of hepatitis C virus 1b for prediction of response to interferon therapy in humans)
IT **Gene, microbial**
Viral RNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(method to detect substitutions in interferon-sensitivity-detg. region of hepatitis C virus 1b for prediction of response to interferon therapy in humans)
IT **Antiviral agents**
(**resistance to;** method to detect substitutions in interferon-sensitivity-detg. region of hepatitis C virus 1b for prediction of response to interferon therapy in humans)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L76 ANSWER 16 OF 30 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:409563 HCAPLUS
DOCUMENT NUMBER: 137:45842
TITLE: Genes of major histocompatibility complex class II influence chronic C hepatitis treatment with interferon in hemodialysis patients
AUTHOR(S): Dincer, D.; Besisik, F.; Oguz, F.; Sever, M. Sukru; Kaymakoglu, S.; Cakaloglu, Y.; Demir, K.; Turkoglu, S.; Carin, M.; Okten, A.
CORPORATE SOURCE: Division of Gastroenterohepatology, Medical Faculty, Istanbul, Turk.
SOURCE: International Journal of Artificial Organs (2001), 24(4), 212-214
CODEN: IJAODS; ISSN: 0391-3988
PUBLISHER: Wichtig Editore
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The prevalence of anti-HCV among patients on hemodialysis is consistently higher than in the general population, indicating that patients on hemodialysis programs are at risk of acquiring HCV infection. The response to interferon alpha 2b (IFN -.alpha. 2b) therapy in chronic C hepatitis depends on viral and host factors. We treated 22 chronic C hepatitis uremic patients with IFN -.alpha. 2b (3 MU three times a week) and compared interferon responsive and unresponsive patients with regard to HLA II genes. HLA II genes were investigated by PCR-SSP low resoln., anti-HCV with ELISA II and HCV-RNA with reverse transcriptase "nested" PCR. Findings: HLA DRB1*13 is 50% pos. in the non-responder group (four women, four men, mean age; 28.8 .+-. 11.9 yr) and 7% in the responder group (five women, nine men, mean age; 32.2 .+-. 7.8 yr) ($p<0.05$). There was no difference with respect to HLA genes between controls (six women, eight men, mean age; 29.5 .+-. 12.8 yr) and patients (nine women, 13 men, mean age; 31.0 .+-. 9.3 yr) (HLA DRB1*13 is 28% and 22% pos., resp.). We conclude that major histocompatibility complex class II genes influence the outcome of chronic C hepatitis treatment with IFN -.alpha. 2b.

CC 15-7 (Immunochemistry)
Section cross-reference(s): 1

IT **Gene, animal**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HLA-DRB; genes of major histocompatibility complex class II influence interferon treatment of chronic C hepatitis hemodialysis patients)

IT **Gene, animal**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HLA; genes of major histocompatibility complex class II influence interferon treatment of chronic C hepatitis hemodialysis patients)

IT **Drug resistance**
(**antiviral**; genes of major histocompatibility complex class II influence interferon treatment of chronic C hepatitis hemodialysis patients)

IT **Antiviral agents**
Hepatitis C virus
Human
(genes of major histocompatibility complex class II influence interferon treatment of chronic C hepatitis hemodialysis patients)

IT **Antiviral agents**
(**resistance to**; genes of major histocompatibility complex class II influence interferon treatment of chronic C hepatitis hemodialysis patients)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L76 ANSWER 17 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:128121 HCAPLUS
DOCUMENT NUMBER: 136:293289
TITLE: Efficacy of INN therapy based on duration period of negative HCV-RNA during IFN administration
AUTHOR(S): Arase, Yasuji; Ikeda, Kenji; Chayama, Kazuaki; Murashima, Naoya; Tsubota, Akihito; Suzuki, Yoshiyuki; Saitoh, Satoshi; Kobayashi, Masahiro; Kobayashi, Mariko; Suzuki, Fumitaka; Kumada, Hiromitsu
CORPORATE SOURCE: Department of Gastroenterology, Toranomon Hospital, Tokyo, 105, Japan
SOURCE: Hepatology Research (2001), 19(1), 22-30
CODEN: HPRSFM; ISSN: 1386-6346
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We assessed the relationship between the duration period of neg. hepatitis C virus (HCV)-RNA during interferon (IFN) therapy and the efficacy after prolonged IFN therapy in patients with HCV-genotype 1b and high virus load of more than 1 mega equiv./mL (Meq/mL) retrospectively. A total of 100 patients who had HCV-genotype 1b and a high virus load of more than 1 Meq/mL and were treated with natural IFN-.alpha. for more than 12 mo were enrolled in this trial. These patients were given 6 MU of IFN daily for 8 wk, followed by three times weekly for another more than 44 wk. The HCV-RNA pattern during IFN therapy according to neg. or pos. of the serum HCV-RNA by reverse transcription nested polymerase chain reaction (RT-nested PCR) from 2 mo after the initiation of IFN to the termination of IFN were classified as follows: group 1: const. neg. HCV-RNA (n = 41 cases), group 2: const. pos. HCV-RNA (n = 35 cases), group 3: HCV-RNA pattern except for group 1 or group 2 (n = 24 cases). A complete response (CR) was defined as neg. HCV-RNA by RT-nested PCR at two points, 3 and 6 mo after the completion of IFN therapy. CR rate was 58.5% (24 cases) in group 1, but CR rate in group 2 or group 3 was 0%. In group 1, the CR rate was 100% (10/10) in patients with neg. HCV-RNA constantly for period of more than 24 mo during IFN therapy. On the other hand, all patients who had pos. HCV-RNA 2 mo after the initiation of IFN did not get CR. In conclusion, it seems to us that the attainment of constantly neg. HCV-RNA for the period of more than 24 mo during IFN therapy is highly related to CR.
CC 15-5 (Immunochemistry)
IT Antiviral agents
Hepatitis C virus
Human
(efficacy of IFN therapy based on duration period of neg. HCV-RNA during IFN administration)
IT **Gene, microbial**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hepatitis C virus genotype 1b; efficacy of IFN therapy based on duration period of neg. HCV-RNA during IFN administration)
IT **Antiviral agents**
(**resistance to**; efficacy of IFN therapy based on duration period of neg. HCV-RNA during IFN administration)
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L76 ANSWER 18 OF 30 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-45197 DRUGU M T

TITLE: Chronic viral hepatitis.
AUTHOR: Alexander G; Walsh K
LOCATION: Cambridge, U.K.
SOURCE: Int.J.Clin.Pract. (54, No. 7, 450-56, 2000) 1 Fig. 92 Ref.
ISSN: 1368-5031
AVAIL. OF DOC.: Department of Medicine, Box 210, Addenbrooke's Hospital, Cambridge CB2 2QQ, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Chronic hepatitis-B virus (HBV), **hepatitis-C** virus (**HCV**) and hepatitis-delta virus (HDV) infections are reviewed. There are now an estimated 300 million carriers of **HCV** worldwide, and the infection is fast becoming the leading indication for liver transplantation. IFN-alpha monotherapy has a low success rate in **HCV**, but the combination of IFN-alpha and ribavirin is effective in about 40% of patients. No anti-**HCV** vaccine exists. HBV is also widely prevalent, and it is an important cause of liver cirrhosis and hepatocellular carcinoma despite the existence of an effective vaccine. IFN-alpha, lamivudine and adefovir dipivoxil are useful treatments. HDV is a defective virus that only replicates in the presence of hepatitis-B surface antigen (HBsAg). No effective treatment exists for HDV.

L76 ANSWER 19 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:681298 HCAPLUS
DOCUMENT NUMBER: 134:146162
TITLE: The protein kinase-interacting domain in the hepatitis C virus envelope glycoprotein-2 gene is highly conserved in genotype 1-infected patients treated with interferon
AUTHOR(S): Polyak, Stephen J.; Nousbaum, Jean-Baptiste; Larson, Anne M.; Cotler, Scott; Carithers, Robert L., Jr.; Gretch, David R.
CORPORATE SOURCE: Department of Laboratory Medicine, University of Washington, Seattle, WA, USA
SOURCE: Journal of Infectious Diseases (2000), 182(2), 397-404
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hepatitis C virus (HCV) envelope glycoprotein-2 inhibits the interferon (IFN)-induced, double-stranded RNA-activated protein kinase (PKR) via the PKR eukaryotic initiation factor-2.alpha. phosphorylation homol. domain (PePHD). The present study examd. the genetic variability of the PePHD in patients receiving IFN therapy. The PePHD from 12 HCV genotype 1 (HCV-1)-infected patients receiving daily IFN therapy was amplified by reverse-transcriptase polymerase chain reaction and analyzed by direct and clonal sequencing. The PePHD was highly conserved in 38 HCV GenBank isolates. There was no difference in pretreatment PePHD sequences isolated from IFN responders vs. nonresponders. The major PePHD quasi-species variant did not change after 6 wk of daily IFN therapy, and in 1 patient the major quasi-species variant did not change during 9 mo of observation. Sequencing of 25 pretreatment PePHD clones from 3 patients confirmed that there was extremely low sequence variability surrounding the PePHD. Thus, the PePHD is highly conserved in HCV-1-infected IFN responders and nonresponders and does not appear to evolve in response to

IFN therapy.
CC 15-5 (Immunochemistry)
Section cross-reference(s): 3, 10, 14
IT **Drug resistance**
(**antiviral**; protein kinase-interacting domain in hepatitis C virus envelope glycoprotein-2 gene is highly conserved in genotype 1-infected patients treated with interferon)
IT **Gene, microbial**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(env; protein kinase-interacting domain in hepatitis C virus envelope glycoprotein-2 gene is highly conserved in genotype 1-infected patients treated with interferon)
IT **Hepatitis C virus**
(protein kinase-interacting domain in hepatitis C virus envelope glycoprotein-2 gene is highly conserved in genotype 1-infected patients treated with interferon)
IT **Antiviral agents**
(**resistance to**; protein kinase-interacting domain in hepatitis C virus envelope glycoprotein-2 gene is highly conserved in genotype 1-infected patients treated with interferon)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L76 ANSWER 20 OF 30 MEDLINE
ACCESSION NUMBER: 2000470448 MEDLINE
DOCUMENT NUMBER: 20345256 PubMed ID: 10886533
TITLE: Genotype and viral load as prognostic **indicators** in the treatment of **hepatitis C**.
AUTHOR: Trepo C
CORPORATE SOURCE: Hepatitis Research Unit and Liver Unit, Hoteldieu Hospital, Lyon, France.
SOURCE: JOURNAL OF VIRAL HEPATITIS, (2000 Jul) 7 (4) 250-7. Ref: 70
Journal code: 9435672. ISSN: 1352-0504.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20000929
AB Interferon-alpha (IFN-alpha), either alone or in combination with ribavirin, is the standard treatment for patients with **hepatitis C**. However, most patients do not achieve a sustained remission with this treatment regimen. A number of studies have demonstrated that genotype, baseline viral load and/or a decrease in viral load early after treatment induction are the major predictive factors for response to treatment with IFN. Patients with **hepatitis C** virus (HCV) genotype 1 are more resistant to treatment with IFN, whereas low viral load at baseline and a marked decline in the HCV RNA level during the first 2-12 weeks of IFN therapy are associated with enhanced treatment efficacy. These variables could potentially be used to develop treatment algorithms that tailor therapies for specific clinical situations. Continued development and refinement of such algorithms would facilitate

both the selection of patients who are most likely to benefit from therapy and the development of optimal treatment regimens for different patient groups. Predictive factors will also enable clinicians to identify subsets of patients who are not expected to respond well to current treatment. The development of new delivery methods for IFN that produce sustained antiviral pressure may provide a means of treating these previously difficult-to-treat patient groups.

CT Check Tags: Human
Algorithms
Antiviral Agents: TU, therapeutic use
Drug Resistance, Microbial: GE, genetics
Genotype
Hepacivirus: DE, drug effects
Hepacivirus: GE, genetics
Hepatitis C: DI, diagnosis
***Hepatitis C: DT, drug therapy**
***Hepatitis C: VI, virology**
Interferon Type I, Recombinant: TU, therapeutic use
Prognosis
Ribavirin: TU, therapeutic use
Variation (Genetics)

RN 36791-04-5 (Ribavirin)
CN 0 (Antiviral Agents); 0 (Interferon Type I, Recombinant)

L76 ANSWER 21 OF 30 MEDLINE
ACCESSION NUMBER: 2000184084 MEDLINE
DOCUMENT NUMBER: 20184084 PubMed ID: 10717257
TITLE: The molecular basis for responsiveness to anti-viral therapy in hepatitis C.
AUTHOR: Polyak S J; Gerotto M
CORPORATE SOURCE: Department of Laboratory Medicine, University of Washington, Seattle, USA.
CONTRACT NUMBER: AI/DK 41320-02 (NIAID)
SOURCE: FORUM, (2000 Jan-Mar) 10 (1) 46-58. Ref: 97
Journal code: 9315183. ISSN: 1121-8142.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000404

AB Hepatitis C virus (HCV) infection is an important clinical problem, with a world-wide prevalence of approximately 1-2%. HCV infection is associated with an increased risk for the development of severe liver disease. HCV is inherently resistant to anti-viral therapy with interferon (IFN). The virus circulates in infected individuals as a mixture of related, yet genetically distinct variants, or quasispecies. Many studies have implicated HCV quasispecies in IFN responsiveness. Effective containment of HCV quasispecies mutation and selection through more aggressive therapy (e.g. daily induction), combination therapy (e.g. IFN plus ribavirin), or longer lasting therapy (e.g. pegylated IFN) is required for IFN responsiveness. Recently, several HCV proteins including the non-structural 5A and envelope **gene** 2-glycoprotein have been implicated in HCV anti-viral resistance. It is likely that multiple HCV

genes disrupt IFN-induced anti-viral responses at many levels and that these virus-host cell interactions are associated with IFN resistance. Characterisation of HCV-encoded mechanisms of anti-viral resistance has important implications for the development of new anti-virals.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Antiviral Agents: AD, administration & dosage
***Antiviral Agents: TU, therapeutic use**
Drug Combinations
Drug Resistance, Microbial
***Hepacivirus: DE, drug effects**
Hepacivirus: GE, genetics
*Hepatitis C: DT, drug therapy
Interferons: AD, administration & dosage
Interferons: TU, therapeutic use
Liver Diseases: VI, virology
Molecular Biology
Mutation: GE, genetics
Phosphoproteins: GE, genetics
Ribavirin: AD, administration & dosage
Ribavirin: TU, therapeutic use
Risk Factors
Selection (Genetics)
Viral Envelope Proteins: GE, genetics
Viral Nonstructural Proteins: GE, genetics

RN 157184-61-7 (hepatitis C virus envelope 2 protein); 36791-04-5 (Ribavirin); 9008-11-1 (Interferons)

CN 0 (Antiviral Agents); 0 (Drug Combinations); 0 (Phosphoproteins); 0 (Viral Envelope Proteins); 0 (Viral Nonstructural Proteins)

L76 ANSWER 22 OF 30 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 3

ACCESSION NUMBER: 1999:113845 HCAPLUS
DOCUMENT NUMBER: 130:163166
TITLE: Test vectors containing hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for determining antiviral susceptibility and resistance and for antiviral screening
INVENTOR(S): Capon, Daniel J.; Whitcomb, Jeannette M.; Parkin, Neil T.
PATENT ASSIGNEE(S): Virologic, Inc., USA
SOURCE: PCT Int. Appl., 128 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906597	A1	19990211	WO 1998-US15967	19980730

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9888976 A1 19990222 AU 1998-88976 19980730
EP 1012334 A1 20000628 EP 1998-940779 19980730
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
JP 2001512036 T2 20010821 JP 2000-505336 19980730
PRIORITY APPLN. INFO.: US 1997-903507 A 19970730
WO 1998-US15967 W 19980730

AB This invention provides a method for detg. susceptibility for an HCV or HCMV anti-viral drug comprising: (a) introducing a resistance test vector comprising a patient-derived segment and an indicator gene into a host cell; (b) culturing the host cell from (a); (c) measuring expression of the indicator gene in a target host cell, and (d) comparing the expression of the indicator gene from (c) with the expression of the indicator gene measured when steps (a-c) are carried out in the absence of the anti-viral drug, wherein a test concn. of the anti-viral drug is present at steps (a-c); at steps (b-c); or at step (c). This invention also provides a method for detg. HCV or HCMV anti-viral drug resistance in a patient comprising: (a) detg. anti-viral drug susceptibility in the patient at a first time using the susceptibility test described above, wherein the patient-derived segment is obtained from the patient at about said time; (b) detg. anti-viral drug susceptibility of the same patient at a later time; and (c) comparing the anti-viral drug susceptibilities detd. in step (a) and (b), wherein a decrease in anti-viral drug susceptibility at the later time compared to the first time indicates development or progression of anti-viral drug resistance in the patient. This invention also provides a method for evaluating the biol. effectiveness of a candidate HCV or HCMV anti-viral drug compd. Compns. including resistance test vectors comprising a patient-derived segment comprising an HCV or HCMV gene and an indicator gene and host cells transformed with the resistance test vectors are provided.

IC ICM C12Q001-68
CC 1-1 (Pharmacology)
Section cross-reference(s): 3

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(C; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(E1; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(E2; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)

(NS2; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(NS3; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(NS4; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(NS5; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(UL102; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(UL105; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(UL114; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(UL44; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(UL54; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility

and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(UL57; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(UL70; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(UL80; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(UL84; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(UL97; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Gene, microbial**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(UL98; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Plasmid vectors**
(pCMVHCV-luc; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Plasmid vectors**
(pT7HCV-luc1; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Plasmid vectors**
(pT7HCV-luc2; test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. antiviral susceptibility and resistance and for antiviral screening)

IT **Antiviral agents**
Drug resistance
Hepatitis C virus

Human herpesvirus 5
(test vectors contg. hepatitis C or human cytomegalovirus nucleic acid and indicator gene and methods for detg. **antiviral** susceptibility and resistance and for **antiviral** screening)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L76 ANSWER 23 OF 30 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-038959 [03] WPIX
DOC. NO. CPI: C2000-010061
TITLE: Treating liver diseases with interferon-alpha5 or nucleic acid encoding it, particularly chronic **hepatitis C**.
DERWENT CLASS: B04
INVENTOR(S): CIVEIRA MURILLO, M P; LEOZ, E L; VALTUENA, J P; LARREA LEOZ, E; PRIETO VALTUENA, J
PATENT ASSIGNEE(S): (CIEN-N) INST CIENTIFICO & TECNOLOGICO NAVARRA; (CIEN-N) INST CIENTIFICO & TECNOLOGICO NAVARRA SA; (PARA-N) FUNDACION PARA INVESTIGACION MEDICA APLI; (INVE-N) FUNDACION INVESTIGACION MEDICA APLICADA
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9958143	A1	19991118	(200003)*	ES	33
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
ES 2138565	A1	20000101	(200008)		
AU 9937111	A	19991129	(200018)		
ES 2138565	B1	20000816	(200047)		
BR 9911774	A	20010206	(200111)		
EP 1077068	A1	20010221	(200111)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
CN 1307482	A	20010808	(200173)		
EP 1077068	B1	20020327	(200222)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2002514606	W	20020521	(200236)		30
DE 69901099	E	20020502	(200237)		
EP 1077068	B9	20021002	(200272)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
ES 2174604	T3	20021101	(200279)		
AU 753463	B	20021017	(200280)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9958143	A1	WO 1999-ES134	19990513
ES 2138565	A1	ES 1998-1003	19980513
AU 9937111	A	AU 1999-37111	19990513

ES 2138565	B1	ES 1998-1003	19980513
BR 9911774	A	BR 1999-11774	19990513
		WO 1999-ES134	19990513
EP 1077068	A1	EP 1999-919282	19990513
		WO 1999-ES134	19990513
CN 1307482	A	CN 1999-807866	19990513
EP 1077068	B1	EP 1999-919282	19990513
		WO 1999-ES134	19990513
JP 2002514606	W	WO 1999-ES134	19990513
		JP 2000-547994	19990513
DE 69901099	E	DE 1999-601099	19990513
		EP 1999-919282	19990513
		WO 1999-ES134	19990513
EP 1077068	B9	EP 1999-919282	19990513
		WO 1999-ES134	19990513
ES 2174604	T3	EP 1999-919282	19990513
AU 753463	B	AU 1999-37111	19990513

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9937111	A	Based on	WO 9958143
BR 9911774	A	Based on	WO 9958143
EP 1077068	A1	Based on	WO 9958143
EP 1077068	B1	Based on	WO 9958143
JP 2002514606	W	Based on	WO 9958143
DE 69901099	E	Based on	EP 1077068
		Based on	WO 9958143
EP 1077068	B9	Based on	WO 9958143
ES 2174604	T3	Based on	EP 1077068
AU 753463	B	Previous Publ.	AU 9937111
		Based on	WO 9958143

PRIORITY APPLN. INFO: ES 1998-1003 19980513

AB WO 9958143 A UPAB: 20000118

NOVELTY - Use of interferon alpha 5 (I), the sequence (II) that encodes it, and/or essentially similar sequences to prepare compositions for treatment of hepatic diseases.

ACTIVITY - **Antiviral**; anticancer; antiproliferative.

MECHANISM OF ACTION - The method restores the level of (I), which is reduced in diseased liver cells, to normal.

USE - The method is specifically used to treat (i) chronic **hepatitis C**; (ii) cirrhosis of viral origin and (iii) hepatocellular carcinoma.

ADVANTAGE - The method is effective against viral liver disease at various stages of progression.

Dwg.0/3

L76 ANSWER 24 OF 30 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:516135 HCAPLUS

DOCUMENT NUMBER: 131:183034

TITLE: Molecular virology update of hepatitis C virus

AUTHOR(S): Hotta, Hak

CORPORATE SOURCE: Sch. Med., Kobe Univ., Japan

SOURCE: Saishin Igaku (1999), 54(8), 1836-1843
CODEN: SAIGAK; ISSN: 0370-8241

PUBLISHER: Saishin Igakusha

DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 20 refs., on the genome structure of hepatitis C virus (HCV) and gene products, oncogenic activity and its mechanism of HCV core proteins, possible roles of NS3 nonstructural protein-p53 tumor suppressor interactions in hepatocarcinogenesis, and suppression of antiviral activity of interferon (IFN) by NS 5A and its mechanism.
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3, 10
IT **Antiviral agents**
Drug resistance
Genome
Hepatitis C virus
Molecular association
Transformation, neoplastic
(mol. virol. update of hepatitis C virus)
IT **Gene, microbial**
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(mol. virol. update of hepatitis C virus)

L76 ANSWER 25 OF 30 MEDLINE
ACCESSION NUMBER: 2000075230 MEDLINE
DOCUMENT NUMBER: 20075230 PubMed ID: 10607252
TITLE: Evidence for sequence selection within the non-structural 5A **gene** of hepatitis C virus type 1b during unsuccessful treatment with interferon-alpha.
AUTHOR: Gerotto M; Dal Pero F; Sullivan D G; Chemello L; Cavalletto L; Polyak S J; Pontisso P; Gretch D R; Alberti A
CORPORATE SOURCE: Department of Clinical and Experimental Medicine, University of Padua, Italy.
SOURCE: JOURNAL OF VIRAL HEPATITIS, (1999 Sep) 6 (5) 367-72.
Journal code: 9435672. ISSN: 1352-0504.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000720
Last Updated on STN: 20000720
Entered Medline: 20000713
AB Resistance of the hepatitis C virus (HCV) to interferon-alpha (IFN-alpha) therapy in patients with hepatitis C may be genetically controlled by an IFN sensitivity-determining region (ISDR) within the non-structural 5A (NS5A) **gene**. To assess whether HCV 1b strains carrying a 'resistant' type of ISDR are selected during unsuccessful IFN therapy, we analysed the evolution of the NS5A quasispecies, as detected by the clonal frequency analysis technique, and of the ISDR sequence by nucleotide sequence determination, in 11 patients showing no virological response during two consecutive cycles of IFN-alpha therapy. IFN-resistant patients had a homogeneous ISDR quasispecies with sequences identical to those described as 'resistant-' or 'intermediate-' type ISDR. After retreatment with IFN, further selection towards a homogeneous viral population was observed and 10 out of 11 patients had only one variant of HCV with no or just one single amino acid mutation within the ISDR sequence. Treatment and retreatment with IFN was associated in our non-responder patients with evolution of the ISDR quasispecies towards a rather homogeneous viral population carrying a conserved or minimally

mutated ISDR motif, supporting the idea that this motif may be relevant for IFN resistance in HCV 1b-infected individuals.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
Amino Acid Sequence
***Antiviral Agents: PD, pharmacology**
Antiviral Agents: TU, therapeutic use
Drug Resistance, Microbial: GE, genetics
Hepacivirus: CL, classification
***Hepacivirus: DE, drug effects**
Hepacivirus: GE, genetics
*Hepatitis C: DT, drug therapy
Hepatitis C: VI, virology
*Interferon-alpha: PD, pharmacology
Interferon-alpha: TU, therapeutic use
Middle Age
Molecular Sequence Data
Sequence Analysis, DNA
Viral Nonstructural Proteins: CH, chemistry
Viral Nonstructural Proteins: DE, drug effects
*Viral Nonstructural Proteins: GE, genetics

CN 0 (Antiviral Agents); 0 (Interferon-alpha); 0 (NS-5 protein, hepatitis C virus); 0 (Viral Nonstructural Proteins)

L76 ANSWER 26 OF 30 MEDLINE
ACCESSION NUMBER: 2000075228 MEDLINE
DOCUMENT NUMBER: 20075228 PubMed ID: 10607250
TITLE: The non-structural 5A protein of hepatitis C virus.
AUTHOR: Pawlotsky J M; Germanidis G
CORPORATE SOURCE: Department of Bacteriology and Virology and INSERM U99, Hopital Henri Mondor, Universite Paris XII, Creteil, France.
SOURCE: JOURNAL OF VIRAL HEPATITIS, (1999 Sep) 6 (5) 343-56. Ref: 122
Journal code: 9435672. ISSN: 1352-0504.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000720
Last Updated on STN: 20000720
Entered Medline: 20000713

AB The non-structural (NS)5A protein of hepatitis C virus (HCV) is cleaved, after translation, by the NS3-encoded zinc-dependent serine proteinase, from the NS4B protein upstream and the NS5B protein downstream. The released, mature NS5A protein is a 56 000 MW phosphoprotein (p56), which also exists within infected cells in a hyperphosphorylated form (p58). The NS5A **gene** has a quasispecies distribution, meaning that various NS5A sequences co-exist, in various proportions, in infected individuals. HCV NS5A appears to be located in cytoplasmic membranes surrounding the nucleus. Its precise functions are not known. HCV non-structural proteins, including NS5A, form a large multiprotein replication complex, which probably directs the replication of the HCV genome. HCV NS5A lacking the 146 N-terminal amino acids is a potent transcriptional activator in vitro. NS5A can also bind to single-strand

RNA-dependent protein kinase (PKR) and inhibit its antiviral function. An 'interferon (IFN) sensitivity-determining region' has recently been postulated in the NS5A protein central region in hepatitis C virus (HCV) genotype 1b, but strongly conflicting evidence has been published. In fact, there would seem to be no such region in the NS5A protein, even though NS5A plays an important and complex role in HCV resistance to IFN. Structure-function studies are required to identify precisely how NS5A and IFN interact.

CT Check Tags: Human
Amino Acid Sequence
***Antiviral Agents: PD, pharmacology**
Drug Resistance, Microbial
***Hepacivirus**
Hepacivirus: CL, classification
Hepacivirus: DE, drug effects
Hepacivirus: GE, genetics
Hepacivirus: ME, metabolism
Hepatitis C: VI, virology
*Interferon-alpha: PD, pharmacology
Molecular Sequence Data
*Viral Nonstructural Proteins
Viral Nonstructural Proteins: CH, chemistry
Viral Nonstructural Proteins: GE, genetics
Viral Nonstructural Proteins: ME, metabolism
Virus Replication

CN 0 (Antiviral Agents); 0 (Interferon-alpha); 0 (NS-5 protein, hepatitis C virus); 0 (Viral Nonstructural Proteins)

L76 ANSWER 27 OF 30 MEDLINE
ACCESSION NUMBER: 1998184511 MEDLINE
DOCUMENT NUMBER: 98184511 PubMed ID: 9525599
TITLE: Interferon resistance of hepatitis C virus genotype 1b: relationship to nonstructural 5A **gene** quasispecies mutations.
AUTHOR: Pawlotsky J M; Germanidis G; Neumann A U; Pellerin M; Frainais P O; Dhumeaux D
CORPORATE SOURCE: Department of Bacteriology and Virology, Hopital Henri Mondor, Universite Paris XII, Creteil, France.. pawlotsky@univ-paris12.fr
SOURCE: JOURNAL OF VIROLOGY, (1998 Apr) 72 (4) 2795-805. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980430
Last Updated on STN: 19980430
Entered Medline: 19980417

AB A 40-amino-acid sequence located in the nonstructural 5A (NS5A) protein of hepatitis C virus genotype 1b (HCV-1b) was recently suggested to be the interferon sensitivity-determining region (ISDR), because HCV-1b strains with an ISDR amino acid sequence identical to that of the prototype strain HCV-J were found to be resistant to alpha interferon (IFN-alpha) whereas strains with amino acid substitutions were found to be sensitive (N. Enomoto, I. Sakuma, Y. Asahina, M. Kurosaki, T. Murakami, C. Yamamoto, N. Izumi, F. Marumo, and C. Sato, J. Clin. Invest. 96:224-230, 1995; N. Enomoto, I. Sakuma, Y. Asahina, M. Kurosaki, T.

Murakami, C. Yamamoto, Y. Ogura, N. Izumi, F. Marumo, and C. Sato, N. Engl. J. Med. 334:77-81, 1996). We used single-strand conformation polymorphism (SSCP) analysis, combined with cloning and sequencing strategies, to characterize NS5A quasispecies in HCV-1b-infected patients and determine the relationships between pre- and posttreatment NS5A quasispecies mutations and the IFN-alpha sensitivity of HCV-1b. The serine residues involved in phosphorylation of NS5A protein were highly conserved both in the various patients and in quasispecies in a given patient, suggesting that phosphorylation is important in NS5A protein function. A hot spot for amino acid substitutions was found at positions 2217 to 2218; it could be the result of either strong selection pressure or tolerance to these amino acid replacements. The proportion of synonymous mutations was significantly higher than the proportion of nonsynonymous mutations, suggesting that genetic variability in the region studied was the result of high mutation rates and viral replication kinetics rather than of positive selection. Sustained HCV RNA clearance was associated with low viral load and low nucleotide sequence entropy, suggesting (i) that the replication kinetics when treatment is started plays a critical role in HCV-1b sensitivity to IFN-alpha and (ii) that HCV-1b resistance to IFN-alpha could be conferred by numerous and/or related mutations that could be patient specific and located at different positions throughout the viral genome and could allow escape variants to be selected by IFN-alpha-stimulated immune responses. No NS5A sequence appeared to be intrinsically resistant or sensitive to IFN-alpha, but the HCV-J sequence was significantly more frequent in nonresponder quasispecies than in sustained virological responder quasispecies, suggesting that the balance between NS5A quasispecies sequences in infected patients could have a subtle regulatory influence on HCV replication.

CT Check Tags: Human; Support, Non-U.S. Gov't
Amino Acid Sequence
***Antiviral Agents: PD, pharmacology**
Antiviral Agents: TU, therapeutic use
Base Sequence
DNA, Viral
Drug Resistance, Microbial: GE, genetics
Evolution, Molecular
Genes, Viral
Genotype
***Hepacivirus: DE, drug effects**
Hepacivirus: GE, genetics
Hepatitis C, Chronic: DT, drug therapy
*Hepatitis C, Chronic: VI, virology
*Interferon Alfa-2a: PD, pharmacology
Interferon Alfa-2a: TU, therapeutic use
Molecular Sequence Data
*Mutation
Phylogeny
Sequence Homology, Amino Acid
Sequence Homology, Nucleic Acid
*Viral Nonstructural Proteins: GE, genetics

RN 76543-88-9 (Interferon Alfa-2a)

CN 0 (Antiviral Agents); 0 (DNA, Viral); 0 (NS-5 protein, hepatitis C virus); 0 (Viral Nonstructural Proteins)

L76 ANSWER 28 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998292494 EMBASE
TITLE: Ribozyme gene therapy for hepatitis C virus infection.

AUTHOR: Welch P.J.; Yei S.; Barber J.R.
CORPORATE SOURCE: J.R. Barber, Immusol Inc., 3050 Science Park Road, San Diego, CA 92121, United States. barber@immusol.com
SOURCE: Clinical and Diagnostic Virology, (15 Jul 1998) 10/2-3 (163-171).
Refs: 15
ISSN: 0928-0197 CODEN: CDVIE8
PUBLISHER IDENT.: S 0928-0197(98)00029-4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background: The development of antiviral drugs for hepatitis C virus (HCV) infection represents a substantial challenge. Similar to human immunodeficiency virus HIV), HCV is highly prone to mutation. It is, therefore, expected that potential HCV therapeutics currently under development, such as protease inhibitors, will suffer from the same shortcomings of HIV therapeutic drugs; the emergence of drug resistant viral mutants. Ribozymes (Rz) are erge enzymatic RNA molecules that can be engineered to specifically target any given RNA molecule. A therapeutic Rz can be manufactured and administered as a drug, or a Rz gene can be delivered and expressed intracellularly by gene therapy. For HCV therapeutics, we favour the gene therapy approach as delivery and in vivo expression of Rz genes will result in a constant and continuous supply of multiple intracellular Rz, offering less opportunity for the development of drug-resistant viral variants. Objectives: To utilise direct intravenous injection of hepatotropic viral vectors to transfer Rz genes directly into the hepatocytcs of HCV-infected patients, resulting in degradation of the HCV positive strand RNA genome, the viral mRNAs, and even the negative strand RNA replication intermediate. We plan to circumvent the emergence of drug-resistant viral mutants by targeting multiple, highly conserved HCV RNA sequences simultaneously with multiple Rz genes expressed from a single vector. Study design: Rzs targeting conserved regions of the HCV positive and negative RNAs were transcribed in vitro and used to cleave HCV target RNAs. The most effective Rzs identified were then incorporated into adeno associated viral (AAV) vectors and adenoviral (AV) vectors and tested for their ability to inhibit HCV core expression in a tissue culture model. Results: Several Rzs targeting highly conserved HCV sequences effectively degraded positive and negative strands of HCV RNA in vitro. Furthermore, substantial inhibition of HCV gene expression was observed in tissue culture using viral vectors to deliver and express Rz genes. Conclusions: Rz gene therapy has potential for the production of anti-viral drugs directed against HCV. Initial studies employing Rz gene therapy to produced anti-viral drugs against HCV have proved successful. Rz gene therapy may be a useful approach to overcome problems associated with anti-HCV drug design, such as the emergence of drug-resistant mutants.
CT Medical Descriptors:
*gene therapy
*hepatitis c: TH, therapy
hepatitis c virus
virus mutation
liver cell
virus vector
gene expression

gene targeting
rna replication
human
nonhuman
conference paper
priority journal
Drug Descriptors:
*ribozyme
***antivirus agent**
proteinase inhibitor
RN (proteinase inhibitor) 37205-61-1

L76 ANSWER 29 OF 30 MEDLINE
ACCESSION NUMBER: 1998412672 MEDLINE
DOCUMENT NUMBER: 98412672 PubMed ID: 9741641
TITLE: Repression of the PKR protein kinase by the hepatitis C virus NS5A protein: a potential mechanism of interferon resistance.
AUTHOR: Gale M J Jr; Korth M J; Katze M G
CORPORATE SOURCE: Regional Primate Research Center and Department of Microbiology, School of Medicine, University of Washington, Seattle 98195-7542, USA.
CONTRACT NUMBER: AI 22646 (NIAID)
AI 41629 (NIAID)
RR 00166 (NCRR)
SOURCE: CLINICAL AND DIAGNOSTIC VIROLOGY, (1998 Jul 15) 10 (2-3) 157-62. Ref: 30
Journal code: 9309653. ISSN: 0928-0197.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981208

AB BACKGROUND: Chronic infection with hepatitis C virus (HCV) is associated with progressive liver damage, including the development of cirrhosis and hepatocellular carcinoma, and HCV is a leading cause of liver dysfunction worldwide. The current therapy for chronic HCV infection, interferon-alpha (IFN), is effective in a minority of HCV-infected patients. Several studies have demonstrated a correlation between therapeutic outcome and the amino acid sequence of a small region of the HCV non-structural 5A (NS5A) **gene** product. It has been suggested that this region, termed the interferon sensitivity-determining region (ISDR), may mediate IFN resistance by directly interacting with one or more cellular proteins associated with the IFN-mediated antiviral response. OBJECTIVES: In an attempt to define the molecular mechanism by which the NS5A protein and the ISDR might contribute to HCV resistance to IFN, we examined whether NS5A could regulate the IFN-induced protein kinase, PKR, a primary mediator of the IFN-induced antiviral response. STUDY DESIGN: Multiple approaches, including in vitro assays using recombinant proteins, the transfection of recombinant clones into cultured cells, and in vivo studies in yeast, were used to examine the interaction of NS5A with PKR, as well as the functional significance of the interaction. An ISDR deletion mutant was prepared to evaluate the

importance of the ISDR in mediating the NS5A-PKR interaction and the requirement of this region for PKR inhibition. RESULTS: NS5A repressed PKR activity through a direct interaction with the protein kinase catalytic domain. Both PKR repression and interaction required the presence of the ISDR. CONCLUSIONS: Inactivation of PKR may be one mechanism by which HCV avoids the antiviral effects of IFN. Thus,therapeutic strategies designed to block the NS5A-PKR interaction may increase the efficacy of IFN therapy in HCV-infected individuals.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
***Antiviral Agents: PD, pharmacology**
***Drug Resistance, Microbial: GE, genetics**
***Hepacivirus: DE, drug effects**
Hepacivirus: GE, genetics
Hepacivirus: ME, metabolism
Hepatitis C: DT, drug therapy
*Interferon-alpha: PD, pharmacology
Viral Nonstructural Proteins: GE, genetics
*Viral Nonstructural Proteins: PD, pharmacology
*eIF-2 Kinase: AI, antagonists & inhibitors
eIF-2 Kinase: GE, genetics

CN 0 (Antiviral Agents); 0 (Interferon-alpha); 0 (NS-5 protein, hepatitis C virus); 0 (Viral Nonstructural Proteins); EC 2.7.1.37 (eIF-2 Kinase)

L76 ANSWER 30 OF 30 MEDLINE
ACCESSION NUMBER: 97201442 MEDLINE
DOCUMENT NUMBER: 97201442 PubMed ID: 9049228
TITLE: Mutations in the nonstructural 5A **gene** of European hepatitis C virus isolates and response to interferon alfa.
COMMENT: Comment in: Hepatology. 1997 Mar;25(3):769-71
AUTHOR: Zeuzem S; Lee J H; Roth W K
CORPORATE SOURCE: Medizinische Klinik II, Klinikum der Johann Wolfgang Goethe-Universitat, Frankfurt a.M., Germany.
SOURCE: HEPATOLOGY, (1997 Mar) 25 (3) 740-4.
Journal code: 8302946. ISSN: 0270-9139.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970327
Last Updated on STN: 19980206
Entered Medline: 19970320

AB The response rate to interferon alfa (IFN-alpha) in patients infected with hepatitis C virus (HCV) genotype 1 isolates is poor. A region associated with sensitivity to IFN has been identified in subtype HCV-1b isolates from Japanese patients in the carboxyterminal half of the nonstructural protein NS5A (between codon 2209 and 2248). HCV-1b isolates with at least four amino acid changes in this region compared with the HCV-1b prototype sequence were sensitive, whereas isolates identical to the prototype sequence were resistant to IFN-alpha. Patients infected with HCV-1b isolates carrying 1 to 3 mutations in NS5A(2209-2248) showed an intermediate response pattern. Because of the large geographical differences observed for HCV it is unknown whether this putative IFN-alpha sensitivity determining region is also predictive for European isolates. We analyzed 32 patients chronically infected with HCV-1a or HCV-1b isolates who were treated with 3 million units of recombinant IFN-alpha three times per week for 1 year. Before initiation, during, and after

treatment serum HCV-RNA levels were assessed by a quantitative reverse-transcription polymerase chain reaction (RT-PCR) assay. The amino acid sequence of NS5A(2209-2248)was determined by direct sequencing of the PCR-amplified HCV genome and was compared with the reference sequence HCV-J. In patients chronically infected with subtype HCV-1a or HCV-1b the initial or sustained response to IFN-alpha was not related to the number of amino acid substitutions in the NS5A(2209-2248) region. In addition, the number of amino acid changes in NS5A(2209-2248) was not related to pretreatment HCV-RNA serum levels. In three patients with a pronounced initial decline of HCV-RNA levels (>3 log) sequence analyses of NS5A(2209-2248) were performed before and after therapy. Compared with the pretreatment amino acid sequence the HCV isolates of these patients revealed more mutations in the NS5A(2209-2248) region after therapy. These findings from European patients indicate that the NS5A(2209-2248) region of HCV does not represent a common interferon sensitivity determining region.

CT Check Tags: Female; Human; Male
Adult
Amino Acid Sequence
***Antiviral Agents: TU, therapeutic use**
Drug Resistance
Europe
Hepacivirus: CL, classification
***Hepacivirus: DE, drug effects**
***Hepacivirus: GE, genetics**
Hepatitis C: BL, blood
*Hepatitis C: DT, drug therapy
Hepatitis C: VI, virology
Hepatitis, Chronic: BL, blood
*Hepatitis, Chronic: DT, drug therapy
Hepatitis, Chronic: VI, virology
*Interferon-alpha: TU, therapeutic use
Middle Age
Molecular Sequence Data
*Mutation: GE, genetics
RNA, Viral: BL, blood
RNA, Viral: DE, drug effects
CN 0 (Antiviral Agents); 0 (Interferon-alpha); 0 (RNA, Viral)

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